CLAIMS

We claim:

1. A method of screening for an inhibitor of an active KIT tyrosine kinase receptor in a cell comprising:

(a) contacting a cell comprising an active KIT tyrosine kinase receptor with a candidate inhibitor; and

(b) detecting KIT activity by using a phosphotyrosine-specific antibody to determine the amount of KIT tyrosine phosphorylation in the presence and in the absence of said inhibitor,

wherein a decrease in KIT tyrosine phosphorylation in the presence of said candidate inhibitor in comparison to the KIT tyrosine phosphorylation in its absence identifies the candidate inhibitor as a KIT inhibitor.

2. The method according to claim 1 wherein said KIT tyrosine kinase receptor is constitutively active.

3. The method according to claim 2 wherein the constitutively active KIT tyrosine kinase receptor has a mutation in the phosphotransferase tyrosine kinase domain.

4. The method according to claim 3 wherein the mutation is in the activation loop of the KIT tyrosine kinase domain.

5. The method according to claim 2 wherein the constitutively active KIT tyrosine kinase receptor has a mutation in the juxtamembrane domain.

6. The method according to claim 5 wherein the mutation is a deletion of amino acids 550-558 of SEQ ID NO:2.

7. The method according to claim 2 wherein the constitutively active KIT tyrosine kinase receptor has a mutation in the extracellular domain.

8. The method according to claim 7 wherein the mutation is a substitution mutation of AY502-503 in SEQ ID NO: 2.

9. The method according to claim 1 wherein the KIT tyrosine kinase receptor comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:2, 4, and 6

10. The method according to claim 9 wherein the KIT tyrosine kinase receptor comprises the amino acid sequence set forth in SEQ ID NO:2.

11. The method according to claim 4 wherein the KIT tyrosine kinase receptor comprises a substituted amino acid at position 816 of SEQ ID NO:2.

12. The method according to claim 11 wherein the substituted amino acid is selected from the group consisting of Valine, Histidine, Phenylalanine, Tyrosine, or Glycine.

13. The method according to claim 12 wherein the substituted amino acid is Valine.

14. The method according to claim 1 wherein the cell comprising the active KIT tyrosine kinase receptor is bound to a solid support.

15. The method according to claim 14 further comprising detecting cellular morphology, cytoskeletal rearrangement, or nuclear staining of said cell in the presence and in the absence of the candidate inhibitor.

16. The method according to claim 1 wherein the phosphotyrosine-specific antibody is selected from the group consisting of a monoclonal antibody, a polyclonal antibody, a chimeric antibody, a humanized antibody, a single-chain antibody, and an antibody fragment.

17. The method according to claim 16 wherein the phosphotyrosine-specific antibody is pY823.

18. The method according to claim 16 wherein the phosphotyrosine-specific antibody binds to an auto-phosphorylation site of said KIT tyrosine kinase receptor.

19. The method according to claim 16 wherein the phosphotyrosine-specific antibody is detectably labeled.

20. The method according to claim 19 wherein the detectable label is a fluorophore or a radiolabel.

21. The method according to claim 1 wherein the detecting step comprises flow cytometry.

22. The method according to claim 1 wherein the active KIT tyrosine kinase receptor is expressed from a heterologous vector.

23. The method according to claim 1 wherein the active KIT tyrosine kinase receptor is endogenous to the cell.

24. The method according to claim 23 wherein the cell is isolated from a tumor.

25. The method according to claim 24 wherein the tumor is selected from the group consisting of a mast cell leukemia, mast cell sarcoma, a germ cell tumor, a gastrointestinal stromal tumor, an acute myeloid leukemia (AML), a chronic myeloid leukemia (CML), a chronic myelomonocytic leukemia (CMML), a sinonasal lymphoma, an ovarian tumor, a breast tumor, a small lung cell carcinoma, a neuroblastoma, and a melanoma.

26. A kit for screening for an inhibitor of active KIT tyrosine kinase receptor comprising a phosphotyrosine antibody and instruction for performing a screen according to claim 1 for said inhibitor.

27. A method of treating a condition selected from the group consisting of mastocytosis, mast cell leukemia, mast cell sarcoma, a germ cell tumor, a gastrointestinal stromal tumor, an acute myeloid leukemia (AML), a chronic myeloid leukemia (CML), a chronic myelomonocytic leukemia (CMML), a sinonasal lymphoma, an ovarian tumor, a breast tumor, a small lung cell carcinoma, a neuroblastoma, and a melanoma, comprising administering an inhibitor identified according to the method of claim 1.

28. A method for designing a treatment regimen for a patient with a mast cell disorder comprising:

(a) isolating a cell from said patient, wherein said cell comprises an active KIT tyrosine kinase receptor;

(b) contacting said cell with a KIT inhibitor identified by the method of claim 1;

(c) detecting KIT activity in said cell using a phosphotyrosine-specific antibody to determine the amount of KIT tyrosine phosphorylation in the presence and in the absence of said inhibitor; and

(d) designing a treatment regimen for said patient which includes administration of the KIT inhibitor that specifically inhibits KIT activity in said patient.